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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/445,328
Filing Date: December 07, 1999
Appellant(s): SAMPATH ET AL.

Erika Takeuchi
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 09/20/2007 appealing from the Office action mailed 09/21/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 2, 5, 6, 8, 9, 11, 12, 14–20, 23, 24, 26, 27, 35–38, 53, 54 (in part), 55 (in part), and 56-65.

Claims 21, 22, 25, 28-34, 54 (in part) and 55(in part) are withdrawn from consideration as not directed to the elected invention.

Appellants elected with traverse the species OP-1, the species the mature form of OP-1, the species pre-renal causes of acute renal failure, the species decreased cardiac output, and the species intravenous administration in the paper mailed 08/06/2002. With respect to claims 54 and 55, appellants' elected the species GFR (glomerular filtration rate) in the reply filed on 03/01/2005.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

Claims 2 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly in view of Kuberasampath and Lefer; and

Claims 2, 53, 58, 61 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly in view of Kuberasampath and Lefer as applied to claims 2 and 53 above, and further in view of Anderson and Brady.

GROUNDS OF REJECTION NOT ON REVIEW

The following grounds of rejection have not been withdrawn by the examiner, but they are not under review on appeal because they have not been presented for review in the appellant's brief.

Claims 5, 6, 8, 9, 11, 12, 14, 23, 24, 26, 27, 35–38, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93).

Claims 15–20, 53–55, 59, 60, 62, 63 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93) as applied to claims 2 and 53, and further in view of Anderson (Chapter 275, in Harrison's Principles Of Internal Medicine, 1980) and Brady (Chapter 236, in Harrison's Principles Of Internal Medicine, 1994).

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 93/04692 KUBERASAMPATH 03-1993

Anderson et al. "Acute Renal Failure", Chapter 275 in Harrison's principles of internal medicine, 9th ed., editors, Kurt J. Isselbacher ... [et al.]. New York : McGraw-Hill, c1980, pages 1291-1299.

Asahina et al. Human osteogenic protein-1 induces both chondroblastic and osteoblastic differentiation of osteoprogenitor cells derived from newborn rat calvaria. J Cell Biol. 1993 Nov;123(4):921-33.

Brady et al. "Acute Renal Failure," Chapter 236, in Harrison's principles of internal medicine. 13th ed., editors, Kurt J. Isselbacher ... [et al.]. New York: McGraw-Hill, 1994, pages 1265-1274.

Kelly et al. Intercellular adhesion molecule-1-deficient mice are protected against ischemic renal injury. J Clin Invest. 1996 Feb 15;97(4):1056-63.

Lefer et al. Anti-ischaemic and endothelial protective actions of recombinant human osteogenic protein (hOP-1). J. Mol. Cell. Cardiol. 1992 Jun;24(6):585-93.

Sampath et al. Recombinant human osteogenic protein-1 (hOP-1) induces new bone formation in vivo with a specific activity comparable with natural bovine osteogenic protein and stimulates osteoblast proliferation and differentiation in vitro. J Biol Chem. 1992 Oct 5;267(28):20352-62.

Vukicevic et al. Induction of nephrogenic mesenchyme by osteogenic protein 1 (bone morphogenetic protein 7). Proc Natl Acad Sci U S A 1996 Aug 20;93(17):9021-6.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 2 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93).

Kelly teaches that ICAM-1 is a key mediator of ischemic acute renal failure likely acting via potentiation of neutrophil-endothelial interactions (Abstract). Kelly shows an improvement of BUN and creatinine levels in ICAM-deficient mice after renal ischemia (page 1057, Figure 3). Kelly proposes that the protection afforded by knockout of the ICAM-1 gene is due to prevention of leukocyte accumulation in the kidney (page 1061, right column, full paragraph 1). The data of Kelly suggest that agents designed to block leukocyte-endothelial interactions mediated via ICAM-1 may be therapeutically effective in the prevention and treatment of acute renal failure (page 1062, left column, full paragraph 2). These data suggest a critical role for leukocytes and adhesion molecules, in particular ICAM-1, in the pathophysiology of ischemic acute renal failure and may have important therapeutic implications for the treatment of acute renal failure in

humans (page 1062, left column, full paragraph 3). Kelly does not teach administering OP-1 to a mammal afflicted with acute renal failure.

Kuberasampath teaches that damage to cells resulting from the effects of an inflammatory response by immune cell mediated tissue destruction has been implicated as the cause of reduced tissue function or loss of tissue function in the kidney (page 1, lines 21-33). Adhering neutrophilic leukocytes produce the humoral factors thought to mediate these damaging effects (page 2, full paragraph 1.) Kuberasampath provides a method for alleviating tissue damage associated with ischemic-reperfusion injury and for modulating the inflammatory responses in general. The method alleviates tissue damage associated with ischemic-reperfusion injury in a human which has suffered from hypoxia or ischemia following cardiac arrest, pulmonary embolus, renal artery occlusion, coronary occlusion or occlusive stroke. See page 7, line 10, through page 8, line 19.

Kuberasampath's method comprises the step of administering to the animal a therapeutically effective amount of a morphogenic protein upon tissue injury, or in anticipation of such injury, for a time and at a concentration sufficient to significantly inhibit or reduce the tissue destructive effects of the inflammatory response, including repairing damaged tissue, and/or inhibiting additional damage thereto (page 9, full paragraphs 1-2).

OP-1 is a morphogen that is useful in the method (page 14, full paragraph 1). Kuberasampath also teaches the mature form of human OP-1 (page 15, lines 1-2), which comprises amino acid residues 330-431 of human OP-1.

It is believed that the morphogens modulate the inflammatory response by modulating the attachment of immune effector cells to the luminal side of the endothelium of blood vessels at or near sites of tissue damage and/or inflammatory lesions. Kuberasampath's method not only relates to a method to reduce or prevent the immune cell-mediated cellular destruction at extravascular sites of recent tissue destruction, but also relates to a method to prevent or reduce the continued entry of immune effector cells into extravascular sites of ongoing inflammatory cascades. The morphogens are also contemplated for use in disrupting the functional interaction of immune effector cells with endothelium where the adhesion molecules are induced by means other than in response to tissue injury. See page 38, line 3, through page 40, line 9.

In addition to inhibiting the tissue destructive effects associated with the inflammatory response, the morphogens further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue (page 40, full paragraph 2).

The morphogen may be provided parenterally, such as by intravenous injection (page 51, lines 8-9). Typical dose ranges are given (paragraph bridging pages 59-60).

OP-1 (page 14, line 30, through page 15, line 17) inhibits the adherence of LTB4 activated PMNs to endothelium (Example 5, pages 74-75) and inhibits cellular and humoral inflammatory reactions (Example 7, pages 78-80).

Lefer teaches that hOP-1 exhibits significant anti-adherent actions on PMNs (page 592, left column, second sentence).

Kuberasampath and Lefer do not teach administering OP-1 to a mammal afflicted with acute renal failure (ARF). However, it would have been obvious to one of ordinary skill in the art at the time of Appellants' invention to administer an agent designed to block neutrophil-endothelial interactions to a mammal afflicted with ARF, as taught by Kelly, and to modify that teaching by administering OP-1, as taught by Kuberasampath and Lefer, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because agents designed to block neutrophil-endothelial interactions may be therapeutically effective in the prevention and treatment of acute renal failure and OP-1 is an agent designed to block neutrophil-endothelial interactions.

BUN and creatinine levels improve in ICAM-deficient mice after renal ischemia (Kelly, page 1057, Figure 3). Therefore, one of ordinary skill in the art would have a reasonable expectation that administering OP-1 to a mammal afflicted with acute renal failure would improve BUN and creatine levels because (1) ICAM-deficient mice were protected from acute renal ischemic injury (Kelly, Abstract), (2) renal leukocyte infiltration was markedly less in ICAM-1-deficient than control mice (Kelly, Abstract), (3) neutrophil-depleted mice were also protected against ischemic renal failure (Kelly, Abstract), and (4) OP-1 is an agent designed to block neutrophil-endothelial interactions (Kuberasampath and Lefer). By definition, BUN and creatine levels are standard markers of kidney function (see claims 54 and 55). The instant specification also defines BUN or creatine as "a standard marker of renal function" (page 11, full paragraph 1). Furthermore, OP-1 further enhances the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue (Kuberasampath, page 40, full paragraph

2). Therefore, one of ordinary skill in the art would have a reasonable expectation of "effecting an improvement in a standard marker of renal function in the mammal afflicted with acute renal failure," as recited in claims 2 and 53.

The limitation "wherein said renal therapeutic agent: (a) induces chondrogenesis in an ectopic bone assay; or (b) prevents, inhibits, delays or alleviates loss of renal function resulting from acute renal failure in an animal of acute renal failure" (claims 2 and 53) only limits the properties of the agent administered and does not limit the claimed method. The OP-1 taught by Kuberasampath is identical to the OP-1 administered in the claimed method. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, the properties of the agent administered that appellant discloses and/or claims are necessarily present in Kuberasampath's OP-1.

The invention is *prima facie* obvious over the prior art.

(10) Response to Argument

It is noted that on page 11 of the brief appellants state that "[t]he examiner rejects claims 2, 53, and 58 as being allegedly obvious over Kelly...in view of Kuberasampath...and Lefer... ." This is not correct because:

(1) Claims 2 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly in view of Kuberasampath and Lefer; and

(2) Claims 58, 61 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly in view of Kuberasampath and Lefer as applied to claims 2 and 53 above, and further in view of Anderson and Brady.

As noted by appellants on page 10 of the Brief, claims 2 and 53, unlike claim 58, are not limited to a pre-renal cause of cause acute renal failure. Thus, claims 2 and 53 are generic to claim 58. Therefore, if claim 58 is found unpatentable, then claims 2 and 53 would also be unpatentable. If claim 58 is found patentable, claims 2 and 53 are not necessarily patentable.

Appellants argue ((1), page 12) that a reasonable expectation of success is lacking because the examiner has failed to show why one skilled in the art would have ignored the scientific literature documenting the adverse renal effects of anti-inflammatory agents, and why he would have selected the anti-inflammatory agent OP-1 to improve renal function in a subject with acute renal failure. In fact, one skilled in the art would have expected that the morphogen OP-1 would not only fail to improve renal function in a subject afflicted with acute renal failure, but also that it would aggravate the renal dysfunction. The skilled artisan would not have expected OP-1 to be the exception among anti-inflammatory agents.

Appellants' arguments have been fully considered but they are not persuasive. There is no evidence of record that OP-1 has any of the adverse renal effects of TGF-β, CsA or NSAIDs or that any of the adverse renal effects of TGF-β, CsA or NSAIDs are mediated through the blocking of neutrophil-endothelial interactions. Therefore, there is no evidence that a skilled artisan would have expected OP-1 to aggravate renal dysfunction. Therefore, the fact that TGF-β, CsA or NSAIDs may decrease renal function, or even to cause outright renal failure, is not a teaching away from using OP-1 to block neutrophil-endothelial interactions in a mammal afflicted with ARF. A skilled artisan would have selected OP-1 to improve renal function in a subject with acute renal failure because the data of Kelly suggest that agents designed to block leukocyte-endothelial interactions may be therapeutically effective in the prevention and

treatment of acute renal failure, and OP-1 blocks leukocyte-endothelial interactions, as taught by Kuberasampath and Lefer.

Appellants argue ((2), page 12) that:

> Anti-inflammatory drugs were known to be detrimental to renal function. At the time the application was filed, it was well-documented in the scientific literature that anti-inflammatory agents reduced, rather than improved, renal function.
>
> On pages 10-16 of the Amendment filed on November 12, 2004, Applicants established that Transforming Growth Factor-β1 (TGF-β1), Cyclosporin A (CsA) and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) were known at the time the subject application was filed to be both (i) anti-inflammatory agents which inhibit ICAM adhesiveness, and (ii) detrimental to renal function. The November 12, 2004 amendment included thirteen scientific publications, as Exhibits A-M, documenting the anti-inflammatory and the renal-adverse side effects of these three agents. Rather than reproducing this section of the previous office action in this appeal brief, Appellants provide a summary of the documented adverse renal effects of these three agents in Table B.

Appellants' arguments have been fully considered but they are not persuasive. The functional differences between OP-1 and TGF-β are well documented: For example,

> OP-1 promotes cell condensations and tubulogenesis in E11.5 metanephric mesenchyme, while TGF-β1 had no effect on metanephric differentiation under identical conditions. The growth of E11.5 cultures, as determined by DNA and protein content, was comparable to both OP-1 treated and untreated control, while TGF-β1 reduced the growth in E11.5 kidney cultures.

Vukicevic et al. Proc Natl Acad Sci U S A. 1996 Aug 20;93(17):9021-6, see page 9023, paragraph bridging left and right columns, and page 9024, paragraph bridging left and right columns.

> Direct comparison of TGF-β1 and hOP-1 in these bone cell cultures indicated that, although both hOP-1 and TGF-β1 promoted cell proliferation and collagen synthesis, only hOP-1 was effective in specifically stimulating markers of the osteoblast phenotype.

Sampath et al. J Biol Chem. 1992 Oct 5;267(28):20352-62, see the Abstract.

> OP-1 induces both chondroblastic and osteoblastic differentiation of osteoprogenitor cells derived from newborn rat calvaria. TGF-β1 fails to induce any hypertrophic chondrocytes, and in combination with OP-1, TGF-β1 blocks OP-1-dependent chondroinduction.

Asahina et al. J Cell Biol. 1993 Nov;123(4):921-33, see the Abstract. Therefore, the structural relatedness of OP-1 and TGF-β is not evidence of functional relatedness.

Furthermore, Exhibit D (Ketteler et al. Curr Opin Nephrol Hypertens. 1994 Jul;3(4):446-52), teaches that the fibrogenic effects of TGF-β in a rat model of acute renal injury model were shown to be due to three actions. First, TGF-β induced the synthesis of the extracellular matrix components that accumulate in glomerulosclerosis. Second, TGF-β decreased the action of the plasmin protease system, which is thought to be important in extracellular matrix turnover. Third, synthesis of β1 integrins, which play an important role in extracellular matrix assembly, was increased in the rat model. Interestingly, the addition of TGF-β to normal glomeruli in culture also increased the synthesis of matrix components, inhibited the plasmin protease system, and upregulated the expression of β1 integrins on the cells' surface. See page 447, right column, first full paragraph. The teachings of Exhibit F (Border. Curr Opin Nephrol Hypertens. 1994 Jan;3(1):54-8) are cumulative with those of Exhibit D with respect to the fibrogenic effects of TGF-β. However, there is no evidence of record that OP-1 possesses any of the fibrogenic effects of TGF-β1. In fact, Kuberasampath (WO 93/04692) recognizes that the morphogens, including OP-1, in contrast to fibrogenic growth factors such as TGF-β, stimulate tissue morphogenesis and do not stimulate fibrosis or scar tissue formation (page 40, last full paragraph; Example 9, pages 83-86), which is further evidence that TGF-β and OP-1 are functionally dissimilar. Therefore, evidence that TGF-β is detrimental to renal function because

excess TGF-β1 induces fibrogenesis, is not evidence that OP-1 is detrimental to renal function because OP-1 does not stimulate fibrosis or scar tissue formation.

Exhibit I (Wissmann et al. J Am Soc Nephrol. 1996 Dec;7(12):2677-81) indicates that the acute reduction in GFR (glomerular filtration rate) caused by Cyclosporine A is most likely the result of [renal] arteriolar vasoconstriction (Abstract). However, there is no evidence of record that OP-1 causes vasoconstriction or that a skilled artisan would expect OP-1 to act as a vasoconstrictor. It is worth noting that, acute cyclosporine-induced renal dysfunction is non-progressive, dose dependent, and reversed by dose reduction or discontinuation (Exhibit I, page 2677, right column, full paragraph 1). In other words, despite an acute reduction in GFR a skilled artisan would continue to use cyclosporine A for immunosuppression.

Exhibit K (Whelton et al. J Clin Pharmacol. 1991 Jul;31(7):588-98) discloses that prostaglandins are vasodilatory and maintain renal perfusion and function. The inhibitory effects of NSAIDs on renal prostaglandin production lead to acute, reversible renal failure in at-risk patients. (page 588, right column, last full paragraph). Many of the renal abnormalities that are encountered as a result of NSAID use can be attributed to the action of these drugs on prostaglandins (page 589, left column, full paragraph 3). The teachings of Exhibit L (Bennett et al. Am J Kidney Dis. 1996 Jul;28(1 Suppl 1):S56-62) are cumulative with those of Exhibit K with respect to the inhibitory effects of NSAIDs on renal prostaglandin production. The teachings of Exhibit M (Murray et al. Prog Drug Res. 1997;49:155-71, Abstract only) are cumulative with those of Exhibits K and L with respect to documenting the adverse renal side effects of NSAIDs in at-risk patients. However, there is no evidence of record that a skilled

artisan would expect OP-1 to act as a vasoconstrictor, or that OP-1 inhibits renal prostaglandin production.

There is no evidence of record that inhibition of neutrophil adherence causes any of the renal side-effects of TGF-β1, CsA, or NSAIDs. Therefore, the argument that a skilled artisan would not expect that OP-1 could be used to treat acute renal failure because some agents that have antiinflammatory effects also have adverse renal effects cannot rebut the *prima facie* case of obviousness.

Appellants argue ((3), page 13) that:

> One skilled in the art would have expected that administration of OP-1 to a mammal afflicted with acute renal failure would reduce, not increase, renal function.
>
> OP-1 shares two key properties with TGF-β1, CsA and NSAIDs: (i) it decreases ICAM adhesiveness and (ii) it decreases PMC activity. OP-1 and TGF-β1 are also members of the TGF-β superfamily of growth factors. The Examiner has focused exclusively on OP-l's anti-inflammatory property as the key attribute in making it a seemingly successful candidate for treating Acute Renal Failure (ARF).
>
> But at the time the application was filed, anti-inflammatory agents were documented to actually cause renal dysfunction, especially in subjects with already impaired renal function. One skilled in the art would have expected that OP-1, just like its counterpart anti-inflammatory agents TGF-β1, CsA and NSAIDs, would further impair renal function in a subject afflicted with acute renal failure. One skilled in the art would have expected that administration of the anti-inflammatory OP-1 polypeptide, based on its anti-inflammatory and neutrophil adhesion- inhibiting properties that it shares with NSAIDs, would reduce, rather than increase, renal function. If anything, the documented anti-renal effects of anti-inflammatory agents taught away from administering anti-inflammatory agents, such as OP-1, to subjects with impaired renal function.
>
> While having the burden of proof, the Examiner has failed to establish why one skilled in the art would have made OP-1 the exception amongst anti-inflammatory agents. He has failed to show why one would have expected OP-1 to be the anomaly and to actually improve renal function where other anti-inflammatory agents failed. The burden of going forward was and is on the Examiner to

> overcome the presumption of lack of reasonable expectation of success legitimately established by applicant using documentary evidence during prosecution. Because he has failed to do so, he has failed to establish a prima facie case of obviousness in accordance with MPEP 706.02(j).

Appellants' arguments have been fully considered but they are not persuasive. The examiner believes that he has already addressed these arguments in response to appellants' arguments at (1) and (2) of the brief. As discussed above:

> The structural relatedness of OP-1 and TGF-β is not evidence of functional relatedness;
>
> OP-1, in contrast to fibrogenic growth factors such as TGF-β, stimulates tissue morphogenesis and does not stimulate fibrosis or scar tissue formation.. Therefore, evidence that excess TGF-β1 induces fibrogenesis, which is detrimental to renal function, is not evidence that OP-1 is detrimental to renal function;
>
> There is no evidence of record that OP-1 causes vasoconstriction, that a skilled artisan would expect OP-1 to act as a vasoconstrictor, or that OP-1 inhibits renal prostaglandin production; and
>
> There is no evidence of record that inhibition of neutrophil adhesiveness causes any of the renal side-effects of TGF-β1, CsA, or NSAIDs.
>
> Therefore, the argument that a skilled artisan would not expect that OP-1 could be used to treat acute renal failure because some agents that have antiinflammatory effects also have adverse renal effects is mere argument and cannot rebut the *prima facie* case of obviousness and reasonable expectation of success.

Appellants argue ((4), page 14) that:

> The examiner's counterarguments fail to address why OP-1 would have been expected to be the exception among anti-inflammatory agents.
>
> ...the burden is on the Examiner, not on applicants, to establish the third prong of the prima facie case of obviousness. It is the Examiner who must who must present evidence why one skilled on the art would have expected a fourth anti-inflammatory agent (OP-1) to be the exception among anti-inflammatories – to show why a fourth anti- inflammatory would be effective in treating acute renal failure when the three others anti-inflammatory agents impair renal function. The

> Examiner wants Appellants to provide evidence that OP-1 had the adverse renal effects of the other anti-inflammatory agents. But this is impossible because Appellants discovered that, contrary to expectation, OP-1 could improve renal function.
>
> (i) The Examiner's position turns the test for obviousness on its head because the standard is the reasonable expectation that the invention would work successfully, and not whether there was the infinitesimal chance that OP-1 might improve renal function contrary to expectation. Since there is no evidence supplied by the Examiner that OP-1 would be effective in treating ARF, and documentary evidence shows that other anti-inflammatories were ineffective, there is no prima facie case of obviousness.
>
> (ii) The question is not whether the possibility exists, no matter how small, that two compounds can have different properties. The question is what properties one skilled in the art would have expected the morphogens to have and why one would have expected OP-1 to be an exception. The claimed invention runs counter to conventional wisdom.
>
> (iii) The Examiner seeks to prematurely shift the burden of proof to Applicants, when the Examiner's own initial burden of proof has not yet been satisfied.

Appellants' arguments have been fully considered but they are not persuasive. To the extent that appellants are arguing that the antiinflammatory agents TGF-β, CsA and NSAIDs have adverse renal effects and would not be used to treat acute renal failure, and therefore one of ordinary skill in the art would not use OP-1 to treat renal failure, the examiner believes that he has already addressed these arguments in response to appellants' arguments at (1) and (2) of the brief.

Furthermore, one of ordinary skill in the art would have a reasonable expectation of success because OP-1 inhibits neutrophil-endothelial interactions, as taught by Kuberasampath and Lefer, and because agents designed to block neutrophil-endothelial interactions may be therapeutically effective in the prevention and treatment of acute renal failure, as taught by Kelly. The examiner does not rely on some standard of "exception" or "anomaly" in order to make the

prima facie case. The examiner believes that he has established a *prima facie* case of reasonable expectation of success and obviousness that appellants have failed to rebut.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 2, 53, 58, 61 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93) as applied to claims 2 and 53 above, and further in view of Anderson (Chapter 275, in Harrison's Principles Of Internal Medicine, 1980) and Brady (Chapter 236, in Harrison's Principles Of Internal Medicine, 1994).

Kelly in view of Kuberasampath and Lefer teach administering OP-1 to a mammal afflicted with acute renal failure, as discussed above. Kelly in view of Kuberasampath and Lefer are silent with respect to the acute renal failure being one arising from a pre-renal cause of acute renal failure (claims 58, 61 and 64), administering the agent continuously during the period of acute renal failure, wherein the period of acute renal failure lasts from one to three weeks (claim 61), and a mammal afflicted with acute renal failure wherein the mammal is afflicted with osteodystrophy (claim 64).

Anderson teaches that impaired cardiac output is a major cause of acute deterioration in renal function (page 1293, Table 275-1).

Brady teaches that low cardiac output is one of the major causes of prerenal acute renal failure (page 1266, Table 236-1). Severe or prolonged hypoperfusion may lead to intrinsic renal azotemia (page 1266, left column, full paragraph 1). Management of acute renal failure should focus on elimination of the causative hemodynamic abnormality or toxin, avoidance of

additional insults, and prevention and treatment of complications (page 1272, right column, full paragraph 3).

Anderson and Brady do not teach administering OP-1 to a mammal afflicted with acute renal failure. However, it would have been obvious to one of ordinary skill in the art at the time of Appellants' invention to administer OP-1 to mammal afflicted with acute renal failure, as taught by Kelly in view of Kuberasampath and Lefer, and to modify that teaching by administering OP-1 to a mammal afflicted with acute renal failure arising from a pre-renal cause of acute renal failure, as recited in claims 58, 61 and 64, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because impaired cardiac output is a major cause of acute deterioration in renal function one of the major causes of prerenal acute renal failure (Anderson, page 1293, Table 275-1), and the management of acute renal failure should focus, in part, on avoidance of additional insults and prevention and treatment of complications (Brady, page 1272, right column, full paragraph 3). One would expect kidney tissue destructive effects from the inflammatory response that ensues from the deprivation of oxygen to the kidney during impaired cardiac output (Kuberasampath, page 7, line 10, through page 8, line 19), and one would expect OP-1 to inhibit the tissue destructive effects associated with the inflammatory response and further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue, according to the teachings of Kuberasampath (page 40, full paragraph 2).

Insofar as Kelly in view of Kuberasampath and Lefer and further in view of Anderson and Brady teach the treatment of acute renal failure in a mammal afflicted with a pre-renal cause of acute renal failure by administering OP-1, then administering the agent continuously during

the period of acute renal failure, wherein the period of acute renal failure lasts from one to three weeks, as recited in claim 61, would have been obvious absent any evidence that this difference is unexpected, unobvious, or critical. This difference is obvious because one of ordinary skill in the art would be motivated to avoid additional kidney tissue insults, such as the tissue destructive effects of an inflammatory response, as much as possible and for as long as possible in order to preserve or restore kidney function as much as possible. Furthermore, Kuberasampath teaches administering a therapeutically effective amount of a morphogenic protein upon tissue injury, or in anticipation of such injury, for a time and at a concentration sufficient to significantly inhibit or reduce the tissue destructive effects of the inflammatory response, including repairing damaged tissue, and/or inhibiting additional damage thereto (page 9, full paragraphs 1-2). Therefore, the determination of the length of treatment is well within the purview of an ordinarily skilled artisan.

Further with respect to claim 64, the specification discloses:

> That is, the subjects for treatment are expected to be otherwise free of indications for morphogen treatment. In some number of cases, however, the subjects may present with other symptoms (e.g., osteodystrophy) for which morphogen treatment would be indicated. Paragraph bridging pages 11-12.

The examiner uses the specification as dictionary for a definition of subjects for treatment. Kelly in view of Kuberasampath and Lefer and further in view of Anderson and Brady do not teach a mammal afflicted with osteodystrophy. However, it would have been obvious to one of ordinary skill in the art at the time of Appellants' invention to administer OP-1 to a mammal afflicted with acute renal failure, the acute renal failure being one arising from a pre-renal cause of acute renal failure, as taught by Kelly in view of Kuberasampath and Lefer and further in view of Anderson and Brady, and to modify this teaching by administering OP-1

to a mammal afflicted with acute renal failure, the acute renal failure being one arising from a pre-renal cause of acute renal failure, wherein the mammal is afflicted with osteodystrophy, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because one of ordinary skill in the art would be motivated to treat the acute renal failure.

The invention is *prima facie* obvious over the prior art.

(10) Response to Argument

Appellants argue ((4)(i)-(iii), page 15) that:

> The Examiner's position turns the test for obviousness on its head. ...there is no evidence supplied by the Examiner that OP-1 would be effective in treating ARF, and documentary evidence shows that other anti- inflammatories were ineffective, there is no prima facie case of obviousness.
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> ...The question, however, is not whether the possibility exists, no matter how small, that two compounds can have different properties. The question is what properties one skilled in the art would have expected the morphogens to have and why one would have expected OP-1 to be an exception. Merely pointing out that OP-1 is a different compound than TGF-β1, CsA or an NSAID, proves nothing. TGF-β1, CsA or an NSAID all have different structures from each other yet they all reduce inflammation and reduce renal function. The common teaching of such prior art is that anti-inflammatories generally have an adverse effect on renal function. The claimed invention runs counter to conventional wisdom.
>
> The Examiner seeks to prematurely shift the burden of proof to Applicants, when the Examiner's own initial burden of proof has not yet been satisfied. Specifically, the Examiner is requiring applicants to prove that OP-1 would not be expected to exhibit the harmful renal effects of other anti-inflammatory agents, when it is the Examiner who bears the initial burden of showing why OP-1 should be considered as the exception amongst anti-inflammatory agents. MPEP 2142 imposes the initial burden on the examiner, and this burden has not been meet.

Appellants' arguments have been fully considered but they are not persuasive. As discussed above, the data of Kelly suggest that agents designed to block neutrophil-endothelial interactions may be therapeutically effective in the prevention and treatment of acute renal

failure. BUN and creatinine levels improve in ICAM-deficient mice after renal ischemia (Kelly, page 1057, Figure 3). Therefore, one of ordinary skill in the art would have a reasonable expectation that administering OP-1 to a mammal afflicted with acute renal failure would improve BUN and creatine levels because (1) ICAM-deficient mice were protected from acute renal ischemic injury (Kelly, Abstract), (2) renal leukocyte infiltration was markedly less in ICAM-1-deficient than control mice (Kelly, Abstract), (3) neutrophil-depleted mice were also protected against ischemic renal failure (Kelly, Abstract), and (4) OP-1 is an agent designed to block neutrophil-endothelial interactions (Kuberasampath and Lefer). By definition, BUN and creatine levels are standard markers of kidney function (see claims 54 and 55). The instant specification also defines BUN or creatine as "a standard marker of renal function" (page 11, full paragraph 1). Furthermore, OP-1 further enhances the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue (Kuberasampath, page 40, full paragraph 2). Therefore, one of ordinary skill in the art would have a reasonable expectation of "effecting an improvement in a standard marker of renal function in the mammal afflicted with acute renal failure," as recited in claims 2, 53, 58, 61 and 64.

Furthermore, it would have been obvious to one of ordinary skill in the art at the time of Appellants' invention to administer OP-1 to mammal afflicted with acute renal failure, as taught by Kelly in view of Kuberasampath and Lefer, and to modify that teaching by administering OP-1 to a mammal afflicted with acute renal failure arising from a pre-renal cause of acute renal failure, as recited in claim 58, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because impaired cardiac output is a major cause of acute deterioration in renal function one of the major causes of prerenal acute renal

failure (Anderson, (page 1293, Table 275-1). The management of acute renal failure should focus, in part, on avoidance of additional insults and prevention and treatment of complications (Brady, page 1272, right column, full paragraph 3). One would expect kidney tissue destructive effects of the inflammatory response that ensues from the deprivation of oxygen to the kidney during impaired cardiac output (Kuberasampath, page 7, line 10, through page 8, line 19), and one would also expect OP-1 to inhibit the tissue destructive effects associated with the inflammatory response and further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue, according to the teachings of Kuberasampath (page 40, full paragraph 2).

The examiner concludes that a *prima facie* case of obviousness has been established. The examiner also concludes that appellants' "documentary evidence" (Exhibits D, F, I, K, L and M) does not rebut the *prima facie* case of obviousness for the reasons discussed above. Briefly,

> The structural relatedness of OP-1 and TGF-β is not evidence of functional relatedness;
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> OP-1, in contrast to fibrogenic growth factors such as TGF-β, stimulates tissue morphogenesis and does not stimulate fibrosis or scar tissue formation.. Therefore, evidence that excess TGF-β1 induces fibrogenesis, which is detrimental to renal function, is not evidence that OP-1 is detrimental to renal function;
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> Unlike CsA and NSAIDS, there is no evidence of record that OP-1 causes vasoconstriction, that a skilled artisan would expect OP-1 to act as a vasoconstrictor, or that OP-1 inhibits renal prostaglandin production; and
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> There is no evidence of record that inhibition of neutrophil adhesiveness causes any of the renal side-effects of TGF-β1, CsA, or NSAIDs.

With respect to claim 61, Appellants argue (page 16) that:

> ... the failure to establish a reasonable expectation of success for the method of claim 58 also applies to the method of claim 61, thus rendering claim 61 nonobvious.
>
> A failure to establish a prima facie case of obviousness for claim 61 also arises from the failure of the Examiner to establish a basis as to how the combination of cited references teaches or suggests all the elements of claim 61. In particular, the Examiner has not shown how the combination of cited references allegedly teaches (i) the treatment of a period of acute renal failure lasting from only one to three weeks; and (ii) the continuous administration of OP-1 during this one to three week period of acute renal failure.
>
> ...The Examiner must specifically point out how all the elements of claim 61, are allegedly taught by the combination of references, must point out how the references could be combined to achieve the claimed method, and must point out why one skilled in the art would have had a reasonable expectation of success in treating acute renal failure by administering the morphogen only during a period of one to three weeks. Since the Examiner has failed to show meet these three burdens, a prima facie case of obviousness has not been made.

Appellants' arguments have been fully considered but they are not persuasive. The examiner believes that he has established a *prima facie* case of reasonable expectation of success and obviousness for claim 58 and that appellants have failed to rebut this *prima facie* case, as discussed above.

Furthermore, the test for obviousness is not whether the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). As indicated above, administering OP-1 continuously during the period of acute renal failure, wherein the period of acute renal failure lasts from one to three weeks, would have been obvious absent any evidence that this difference is unexpected, unobvious, or critical. This difference is obvious because one of ordinary skill in the art would be motivated to avoid additional kidney tissue insults, such as the tissue destructive

effects of an inflammatory response, as much as possible and for as long as possible in order to preserve or restore kidney function as much as possible. Furthermore, Kuberasampath teaches administering a therapeutically effective amount of a morphogenic protein upon tissue injury, or in anticipation of such injury, for a time and at a concentration sufficient to significantly inhibit or reduce the tissue destructive effects of the inflammatory response, including repairing damaged tissue, and/or inhibiting additional damage thereto (page 9, full paragraphs 1-2). Therefore, the determination of the length of treatment is well within the purview of an ordinarily skilled artisan.

With respect to claim 64, Appellants argue (page 17) that:

> ... the failure to establish a reasonable expectation of success for the method of claim 58 also applies to the method of claim 64, rendering claim 64 also nonobvious.
>
> A failure to establish a prima facie case of obviousness also arises from the failure of the Examiner to establish a basis as to how the combination of cited references teaches or suggests the treatment of a subject afflicted with osteodystrophy as recited in claim 64.
>
> The Examiner has not identified any teachings or suggestions in the combination of cited references for treating subjects who are additionally afflicted with osteodystrophy. Instead, the Examiner impermissibly tries to use the specification itself as one of the 103(a) references. The Examiner claims to use "the specification as a dictionary for [the] definition of subjects for treatment" (page 3, lines 20-21 of the Office Action dated September 21, 2006), and concludes that it would have been obvious to treat a subject afflicted with osteodystrophy.
>
> But it is the combination of cited reference, and not the specification of the subject application, that must teach or suggest all the claim elements. This section of the specification states that "[i]n some number of cases, however, the subjects may present with other symptoms (e.g. osteodystrophy) for which morphogen treatment would be indicated." (page 12, lines 5-6). The Examiner cannot use the specification as a reference against itself. The suggestion or teaching to treat subjects afflicted with osteodystrophy must be found in the prior art. And the section of the specification cited by the Examiner is not providing any type of definition. It is showing embodiments of subjects that may be treated with OP-1.

> The Examiner has failed to meet his burden of establishing why treatment of ARF patients additionally afflicted with osteodystrophy is allegedly taught by the prior art, and therefore has failed to make a prima facie case of obviousness under MPEP § 706.020).

Appellants' arguments have been fully considered but they are not persuasive. The examiner believes that he has established a *prima facie* case of reasonable expectation of success and obviousness for claim 58 and that appellants have failed to rebut this *prima facie* case, as discussed above.

Furthermore, the test for obviousness is not whether the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The difference between claims 58 and 64 would have been obvious to one of ordinary skill in the art because it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP-1 to a mammal afflicted with acute renal failure, wherein the mammal is afflicted with osteodystrophy, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because one of ordinary skill in the art would be motivated to treat the acute renal failure.

The examiner believes that he has correctly used the specification as dictionary in order to merely to understand what appellants have claimed. The paragraph bridging pages 11-12 establishes the non-criticality of the "osteodystrophy" limitation.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/David S Romeo/
Primary Examiner, Art Unit 1647

Conferees:

/Robert A. Wax/
TQAS Appeals Specialist, TC 1600

/Gary B. Nickol/
Supervisory Patent Examiner, Art Unit 1646